Airway abnormalities in very early treated infantile-onset Pompe disease: A large-scale survey by flexible bronchoscopy

Chia-Feng Yang1,2 | Dau-Ming Niu1,2 | Shyh-Kuan Tai2,3 | Ting-Hao Wang1,2 | Hsiao-Ting Su4 | Ling-Yi Huang1 | Wen-Jue Soong1,2,5

1Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan
2School of Medicine, National Yang-Ming University, Taipei, Taiwan
3Department of Otolaryngology, Taipei Veterans General Hospital, Taipei, Taiwan
4Department of Audiology and Speech Language Pathology, Mackay Medical College, Taipei, Taiwan
5Children's Hospital, China Medical University, Taichung, Taiwan

Abstract
Early enzyme replacement therapy (ERT) improve long-term outcomes in patients with infantile-onset Pompe disease (IOPD). Our cohort of patients with IOPD at Taipei Veterans General Hospital (TVGH) joined Taiwan Pompe newborn screening program from 2008, testing more than one million newborns until 2018. By 2010, we had established rapid diagnostic strategies. Now, the average age of ERT initiation starts at an average age of <10 days-old, the earliest group in the world. However, they still presented some airway problems. We present a retrospective study focused on airway abnormalities in these patients along 8 years of observation. Fifteen patients with IOPD, who received very early treatment at a mean age of 8.94 ± 3.75 days, underwent flexible bronchoscopy (FB) for dynamic assessment of the whole airway. Long-term clinical outcomes and relevant symptoms of the upper airway were assessed. All patients in the study had varying degrees of severity of upper airway abnormalities and speech disorders. The three oldest children (Age 94, 93, and 88 months, respectively) had poor movement of the vocal cords with reduced abduction and adduction and had silent aspiration of saliva through the glottis during respiration. This is the largest cohort study presented to date about airway abnormalities in very early treated patients with IOPD patients by FB. Despite very early treatment, we observed upper airway abnormalities in these IOPD patients. In IOPD, upper airway abnormalities seem inevitable over time. We suggest early and continuous monitoring for all IOPD patients, even with early and regular treatment.

KEYWORDS
airway abnormalities, flexible bronchoscopy, Pompe disease

1 | INTRODUCTION

Pompe disease (Glycogen Storage Disease type II, OMIM # 232300) is an autosomal recessive lysosomal storage disorder characterized by the deficiency of acid α-glucosidase (GAA; Banugaria et al., 2011). Deficiency of this enzyme leads to a progressive accumulation of glycogen in many types of cells and tissues. A broad spectrum of clinical phenotypes is observed, ranging from severe, rapidly progressive infantile-onset Pompe disease (IOPD) characterized by cardiac involvement to the attenuated, late-onset Pompe disease (LOPD). Early enzyme replacement therapy (ERT) with recombinant human alglucosidase alfa (Myozyme®; Sanofi Genzyme, Boston, MA) can prolong the survival and improve the long-term outcome of patients with Pompe disease. Newborn screening have been proved that it was an effective way to initiate early diagnosis and treatment (Chien et al., 2015). Our series at the Taipei Veterans General Hospital (TVGH) began with the Pompe newborn screening program in 2008, testing approximately two-thirds of the newborn population in Taiwan until
2018. More than 1 million newborns were screened during that time. By 2010, we had established an effective newborn screening program with rapid clinical diagnostic strategies. Almost all of the suspected IOPD infants could be diagnosed correctly within 2 hr and receive ERT with Myozyme within 4 hr of admission (Chien et al., 2015). With such an effective system, we were able to initiate treatment with Myozyme in patients with IOPD at an average age of around 8 days, which is the earliest age reported globally. Comparison of prognostic parameters in our study (collected after 2010) to that of other studies of patients with IOPD suggests that patients receiving early Myozyme in our study had better outcomes (Confaloni et al., 2016; Ebbink et al., 2012; Fuller et al., 2013; Jones et al., 2010; Keeler et al., 2017), including normal cognitive and motor function. All of our patients with IOPD survived without mechanical ventilation, walking devices or gastrostomy tube feeding (Lai et al., 2016; Yang et al., 2014, 2016).

Despite early treatment, we found that even though our patients with IOPD had better outcomes, they still developed some airway, buccal region, and respiratory problems, including easy choking, recurrent otitis media, facial muscle weakness, and articulation disorders. Studies suggest that even with regular Myozyme treatment, patients with IOPD and LOPD still developed respiratory dysfunction that might be attributed to respiratory muscle weakness or CNS neuropathy (Lai et al., 2016; McIntosh et al., 2018; Musumeci et al., 2019; Owens, Wong, Bhattacharya, & Ellaway, 2018).

Respiratory dysfunction is a critical prognostic factor for Pompe disease (Bay et al., 2019; Gupta et al., 2019; McCall & ElMallah, 2019) even with regular treatment with Myozyme. There are limited descriptions of abnormalities of the whole airway. The purpose of this study was to evaluate the abnormalities of the whole airway by FB and study the associated clinical outcomes in very early treated patients with IOPD.

2 | METHODS

2.1 | Study population

Screening for Pompe disease was added to the Taiwan newborn screening program from 2008 nationally. In this nationwide program, dried blood spot (DBS) screening was conducted at Taipei Institute of Pathology and Chinese Foundation of Health newborn screening centers using fluorescence (4-MU) assay; this test was changed to the MS/MS method after 2010 (Chien et al., 2015). At the same time, we also established the effective clinical diagnostic strategies (Chien et al., 2015). The study population included 14 patients with IOPD who were referred by the newborn screening program to the TVGH between January 1, 2010 and December 31, 2018. One patient (I-11) was born at our hospital and diagnosed prenatally according to the result of a sibling study in the same period. All included patients were correctly diagnosed by our clinical diagnostic strategies and received ERT on the same day of admission. They received ERT every other week with Myozyme® (20 mg/kg, biweekly) and were followed up with regularly in our hospital. The mean follow-up period was 55.2 months (range 16–94 months). Informed consent was obtained from the parents. The study protocol was approved by the Institutional Review Board of the TVGH (TVGH-2017-07-035C).

2.2 | FB examination

FB was performed at a mean age of around 22 months (range 1 day to 51 months). The diameter of FB was 2.3 mm. All patients received intravenous sedation, with minimal doses of midazolam (0.05 mg/kg) and ketamine (0.05 mg/kg) for maintaining the patients’ spontaneous breathing ability throughout the procedure. All patients were continuously monitored with electrocardiography, pulse oximetry, and noninvasive blood pressure measurements. Pediatric intensivists and anesthesiologists were on standby during the procedure. For delivering oxygen, a nasopharyngeal catheter (NPC; 6F, 8F, or 10F; depending on body weight) was introduced through one nasal tract and the tip was kept in the oropharynx with its position confirmed by FB. Pure, warmed, and humidified oxygen at a flow rate of 0.3–0.5 L/kg/min was continuously delivered via the nasopharyngeal catheter throughout the procedure. FB examination was performed and the abnormalities of the whole airway were diagnosed by a pediatric pulmonologist certified to perform pediatric FB. The FB video of FB examination was recorded and thoroughly analyzed for all patients.

2.3 | Associated clinical symptoms surveys

Data regarding relevant outcomes such as growth status at the end of the study; longitudinal change of CK (creatine kinase), LDH (lactate dehydrogenase), and AST levels (aspartate aminotransferase); and the heart size (LVMI) were recorded. Associated airway symptoms, including easy choking, recurrent acute otitis media (defined as ≥3 episodes in 6 months, or ≥ 4 episodes in 12 months) and recurrent respiratory tract infections (defined as ≥6 serious diseases in a year) were recorded. Speech disorders were simultaneously tested for patients aged >3 years by the Revised Preschool Language Impairment Scale. Facial muscle weakness was defined by drooping of the lower lip, absence of the nasolabial folds, or ptosis.

2.4 | Data analysis

Data are presented as the median with range and mean ± interquartile range. Wilcoxon rank sum test and Kruskal–Wallis test were used to perform statistical analysis. Analysis of longitudinal data by linear regression of the mean value with the outcome for biochemical parameters yielded a Pearson’s product–moment correlation coefficient. All statistical analyses were performed using the SPSS 15.0 statistics software (SPSS Inc., Chicago, IL) and SigmaStat 3.1 (Jandel Scientific, San Rafael, CA).

3 | RESULTS

The study included 15 patients with IOPD who were diagnosed, treated, and followed-up in the period of January 2008 to December
<table>
<thead>
<tr>
<th>Patient id (sex)</th>
<th>Age at diagnosis (in days)</th>
<th>Age at first ERT (in days)</th>
<th>Age at flexible bronchoscopy (in months)</th>
<th>Age at the end of the study (in months)</th>
<th>Height at the end of the study (in cm) (percentile)</th>
<th>Weight at the end of the study (in kg) (percentile)</th>
<th>Anti-rhGAA antibody titer at the end of observation</th>
<th>GAA mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1 (male)</td>
<td>15 days</td>
<td>15 days</td>
<td>51</td>
<td>94</td>
<td>123.3 (15–50)</td>
<td>27.3 (50–85)</td>
<td>0</td>
<td>c.1935C&gt;A, (p.D645E), homozygous c.1726G&gt;A, (p.G576S), homozygous</td>
</tr>
<tr>
<td>I-5 (male)</td>
<td>7 days</td>
<td>7 days</td>
<td>31</td>
<td>70</td>
<td>110 (3–15)</td>
<td>20.5 (15–50)</td>
<td>0</td>
<td>c.1935 C&gt;A, (p.D645E), heterozygous c.4VS7 + 2T&gt;C, heterozygous c.1726G&gt;A, (p.G576S), heterozygous</td>
</tr>
<tr>
<td>I-6 (female)</td>
<td>10 days</td>
<td>10 days</td>
<td>37</td>
<td>66</td>
<td>110.5 (15–50)</td>
<td>19.6 (15–50)</td>
<td>400</td>
<td>c.1935C&gt;A, (p.D645E), homozygous c.1726G&gt;A, (p.G576S), homozygous</td>
</tr>
<tr>
<td>I-8 (female)</td>
<td>8 days</td>
<td>8 days</td>
<td>17</td>
<td>60</td>
<td>117 (85–97)</td>
<td>25.2 (85–97)</td>
<td>800</td>
<td>c.1935 C&gt;A, (p.D645E), heterozygous c.411_414del(E471fsX5), heterozygous c.1726G&gt;A, (p.G576S), heterozygous</td>
</tr>
<tr>
<td>I-9 (female)</td>
<td>7 days</td>
<td>7 days</td>
<td>17</td>
<td>52</td>
<td>107.9 (50–85)</td>
<td>18.2 (50–85)</td>
<td>100</td>
<td>c.1935C&gt;A, (p.D645E), homozygous c.1726G&gt;A, (p.G576S), homozygous</td>
</tr>
<tr>
<td>I-11# (male)</td>
<td>3 hr</td>
<td>3 hr</td>
<td>1 day</td>
<td>32</td>
<td>98.4 (50–85)</td>
<td>17.7 (85–97)</td>
<td>6.400</td>
<td>c.2303G&gt;C, (p.W746C), heterozygous c.2237G&gt;A, (p.W746X), heterozygous c.1726G&gt;A, (p.G576S), heterozygous</td>
</tr>
<tr>
<td>I-12 (female)</td>
<td>9 days</td>
<td>9 days</td>
<td>1</td>
<td>31</td>
<td>88 (25–50)</td>
<td>11.6 (3–15)</td>
<td>400</td>
<td>c.1411_1414del(E471fsX5), heterozygous c.1843G&gt;A, (p.G615R), heterozygous</td>
</tr>
<tr>
<td>I-13 (female)</td>
<td>8 days</td>
<td>8 days</td>
<td>11 days</td>
<td>26</td>
<td>89.6 (50–85)</td>
<td>12.7 (50–85)</td>
<td>200</td>
<td>c.1935 C&gt;A, (p.D645E), homozygous c.1726G&gt;A, (p.G576S), homozygous</td>
</tr>
</tbody>
</table>

(Continues)
2018 in our series. Fourteen patients were referred by the Taiwan Newborn Screening system and one patient (I-11) was diagnosed prenatally from a sibling study. All of them received FB examination in our hospital and the mean age at FB was 21.95 ± 17.42 months (range 1 day to 51 months). All patients were cross-reactive immunologic material (CRIM)-positive. Patient characteristics such as age at diagnosis, age at first Myozyme, age at FB, age at the end of the study, weight, height, anti-rhGAA antibody titer at the end of observation and GAA gene mutation were given in Table 1. All patients met the rapid diagnostic strategies which were set-up in the institute from 2010(Chien et al., 2015) and received their first Myozyme within 4 hr of admission at a mean age of 8.94 ± 3.75 days, on the same day of diagnosis. The dose of Myozyme was 20 mg/kg every other week. All patients were treated and followed up with in our hospital with a median timeframe of 55.2 ± 24.9 months (range 16–94 months). The mean percentile of height and weight at the end of the study were 49.16 ± 29.05th and 53.23 ± 4.13th, respectively. Both height and weight were in the normal range at the end of the study. The mean titer of the anti-rhGAA antibody titers at the end of observation was 1:1020 (1,020 ± 1,645.68, range 0 to 1:6,400). c.1935 C>A was the most frequent mutation of GAA gene, present as compound heterozygote in six of the patients (I-2, I-3, I-4, I-5, I-8, and I-14) and present as homozygote in another six patients (I-1, I-6, I-7, I-9, I-10, and I-13; Confalonieri et al., 2016; Ebbink et al., 2012); the allele frequency of the mutation was 60%.

During follow-up, left ventricular hypertrophy improved quickly after 4–6 months of treatment and remained, according to the long-term change of left ventricular mass index (LVMI; Figure 1). CK, AST, and LDH levels decreased quickly after a few months of treatment but then increased gradually in some patients (Figure 1). No patient required invasive ventilation or nasogastric or gastrostomy tube for feeding. All patients could also walk normally without walking devices. However, they still developed varying severity of easy choking, recurrent otitis media, signs of facial muscle weakness, and articulation disorders which were observed at the end of the study, age 55.2 ± 24.9 months (range 16–94 months).

During FB, all patients had a narrowed nasal tract and oral cavity (Figure 2a,b). All patients had a compromised oropharynx with posterior displacement of the soft palate and uvula and increased rigidity of the pharyngeal wall and tongue base (Figure 2b). Severity of the compromised oropharynx differed and partially obstructed the forward movement of the FB which required reposturing in all patients. 3/15 patients (I-1 to I-3, Figure 2c,d) had reduced abduction and adduction of the bilateral vocal folds, and had silent penetration or aspiration of saliva through the glottis during respiration. The diagnosis of the abnormalities was confirmed by a pediatric pulmonologist certified to perform and evaluate pediatric FB. For I-2 and I-3, I-2 with GAA gene mutation: c.1935C>A, heterozygous; c.2303C>T, heterozygous; c.1726G>A, heterozygous and I-3 with GAA gene mutation: c.1935C>A, heterozygous; c.1396G>T, heterozygous; c.1726 G>A, heterozygous), CK, AST, and LDH levels significantly increased over time and patients had relatively severe abnormalities of the upper airway with worse movement of the buccal region. For I-1 (GAA gene
mutation: c.1935 C>A; c.1726G>A, homozygous), who presented relative severe abnormalities of the upper airway (The FB video of FB for I-1 is available as Video S1), developed signs of facial muscle weakness with drooping of the lower lip, absence of the nasolabial folds, and mild ptosis, but maintained stable levels of CK, AST, and LDH, remained stable at follow-up.

Among these patients with relatively less severe GAA gene mutation (I-1, I-6, I-7, I-9, I-10, and I-13, GAA gene mutation: c.1935C>A; c.1726G>A, homozygous), all started ERT very early (range 8–15 days), the oldest patient (I-1) showed more severe abnormalities of the upper airway as compared to others. Anti-rhGAA antibody titers at the end of observation have not showed the association with
the progression of the airway abnormalities (Table 1). No patient had significant abnormal findings in the main trachea, carina and bilateral main bronchi (Figure 2e; Table 2).

In two patients (I-11 and I-13), where FB was performed at age 1 and 11 days, respectively, we also found narrowing of the nasal and oral cavity with a compromised oropharynx. The FB video of FB for I-1 and I-11 is available as Video S1. There were varying degrees of upper airway problems, including easy choking (15/15), and recurrent acute otitis media (3/15). None of the patients had recurrent respiratory tract infections. All patients >3 years old (range 47–94 months) had articulation disorders with hyper nasal resonance, consonant substitution, consonant omission, and consonant distortion during speech assessment (Table 2).

Latest photographs of four patients (I-1, I-3, I-11, and I-15) are shown in Figure 3. I-1, the oldest patient (age 94 months at the end of study), started Myozyme at age 15 days, and developed signs of facial muscle weakness, with drooping of the lower lip, absence of the nasolabial folds, and mild ptosis. I-3: Age 88 months, started ERT at age 12 days with slight absence of the nasolabial folds. I-11: Age 32 months, started ERT at age 1 day without significant signs of facial muscle weakness. I-15: Age 16 months, started ERT at age 8 days without significant signs of facial muscle weakness [Color figure can be viewed at wileyonlinelibrary.com]

### DISCUSSION

This is the largest cohort study presented to date about the airway abnormalities in very early treated patients with IOPD by FB. Even receiving early and regular treatment, our patients still showed varying severity of airway problems, such as narrowed nasal tract, narrowed oral cavity, and compromised oropharynx. Some patients also had reduced abduction and adduction movements of the bilateral vocal cords.

### TABLE 2

<table>
<thead>
<tr>
<th>Patient id</th>
<th>Age at FB (in months)</th>
<th>Narrowed nasal tract (FB)</th>
<th>Compromised oropharynx (FB)</th>
<th>Poor vocal cords movement (FB)</th>
<th>Silent saliva aspiration (FB)</th>
<th>Easy choking</th>
<th>Recurrent acute otitis media</th>
<th>Speech disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>51</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>I-2</td>
<td>49</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>I-3</td>
<td>45</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>I-4</td>
<td>32</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>I-5</td>
<td>31</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>I-6</td>
<td>37</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>I-7</td>
<td>24</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>I-8</td>
<td>17</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>I-9</td>
<td>17</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>I-10</td>
<td>13</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>I-11</td>
<td>1 day</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>NR</td>
</tr>
<tr>
<td>I-12</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>NR</td>
</tr>
<tr>
<td>I-13</td>
<td>11 days</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NR</td>
</tr>
<tr>
<td>I-14</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
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<td>NR</td>
</tr>
<tr>
<td>I-15</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: +, present; -, absent, NR, not recorded.

FIGURE 3  Current Photographs of I-1, I-3, I-11, and I-15 I-1: Age 94 months, started ERT at age 15 days with drooping of the lower lip, absence of the nasolabial folds, and mild ptosis. I-3: Age 88 months, started ERT at age 12 days with slight absence of the nasolabial folds. I-11: Age 32 months, started ERT at age 1 day without significant signs of facial muscle weakness. I-15: Age 16 months, started ERT at age 8 days without significant signs of facial muscle weakness [Color figure can be viewed at wileyonlinelibrary.com]
folds, as well as poor control of oropharyngeal movement. Our patients presented silent penetration or aspiration of saliva through the glottis during respiration. Further, 11 patients >3 years old had varying severity of speech disorder.

Previous studies have discussed these airway problems, including speech disorders in Pompe disease (Bay et al., 2019; Ebblink et al., 2012; Musumeci et al., 2019; Owens et al., 2018; Yang et al., 2014). Our study is the first presentation of upper airway problems of early treated IOPD patients by whole airway FB examination. Airway problems are critical in patients with IOPD, even with regular ERT (Ebblink et al., 2012; Yang et al., 2014). Previous studies suggest dysphonia, sleep-disordered breathing, daytime hypercapnia, and the eventual need for nocturnal ventilation in some of these patients (Bay et al., 2019; Ebblink et al., 2012; Keeler et al., 2017; Owens et al., 2018; Yang et al., 2014). Some other studies mention respiratory symptoms, including decreased cough and impaired airway clearance, increase in the risk of acute respiratory illness in these patients (Bay et al., 2019; Fuller et al., 2013; Jones et al., 2010; Owens et al., 2018; Yang et al., 2014). Compared with other reports (Ebblink et al., 2012; Musumeci et al., 2019; Owens et al., 2018; Yang et al., 2014), our patients with early treatment had normal weight and height, without advanced respiratory disorders, recurrent respiratory tract infection, or need of invasive ventilation support in the observation period. No patient reported significant dysphagia at the end of study and only two had symptoms of facial weakness (Figure 3). In our series, early treated IOPD patients had normal cognitive and motor function, all our patients survived without mechanical ventilation, walking devices or gastrostomy tube feeding (Confalonieri et al., 2016; Ebblink et al., 2012; Fuller et al., 2013; Jones et al., 2010; Keeler et al., 2017; Lai et al., 2016; Yang et al., 2014, 2016).

There were, however, still some airway problems, such as easy choking, recurrent otitis media, and speech disorders. Progressive airway disorder is a major cause of morbidity and mortality in Pompe disease, even with treatment (Bay et al., 2019; Gupta et al., 2019; McCall & ElMallah, 2019). Some studies have focused on how to detect, monitor, and mentioned about managing respiratory muscle involvement for optimal patient care (Bay et al., 2019; Turner, Hoyt, Falk, Byrne, & Fuller, 2016), but there is no other study presenting the anatomic airway disorders of patients with IOPD who have received early Myozyme using visual FB, and relate them to patients’ clinical symptoms. Our findings suggest that abnormalities of the upper airway develop even after early and regular ERT, possibly due to an insufficient response of Myozyme.

Speech disorders are common in IOPD patients. Evaluation of speech disorders in our patients suggested varying degrees of hypernasal resonance, consonant substitution, consonant omission, and consonant distortion in all patients 3 years of age and older, even with very early and regular ERT. Previous studies of patients with IOPD suggest speech disorders with consonant substitutions, consonant omissions, cluster reductions, mild to moderate hypernasal resonance, hoarseness, and a wet voice (Yang et al., 2014, 2015, 2016). The speech defect could be due to the compromised muscle strength in the oral cavity and the oropharynx. Our findings of the dynamic airway abnormalities could be the reasons of these upper airway problems and speech disorders in these patients.

FB provided a direct visual examination of the airway and was safe in newborns. Based on our group’s experience, FB is a relatively noninvasive and effective procedure, even for infant babies who received FB examination for different clinical indications (Soong, 2018). In two patients (I-11 and I-13), who underwent FB at age 1 and 11 days, respectively, we still found the narrowed nasal tract and the compromised oropharynx. This finding might suggest the prenatal influence of glycogen accumulation in patients with IOPD.

According to our findings, we may recommend to arrange FB examination simultaneously when patients have a confirmed diagnosis of IOPD and follow-up every year.

For these 15 patients with IOPD, no significant abnormal finding in the lower airway was observed. We will continue to follow up regularly
with these patients to detect any changes of the lower airway to apply timely intervention as soon as possible (Zeng et al., 2017).

Compared to other imaging modalities, FB for patients with spontaneous breathing ability throughout the procedure is much more feasible and helps detect dynamic changes in the whole airway. It might be more reliable for assessing the functional abnormalities of the airway than computed tomography or magnetic resonance imaging of the airway and chest. Adequate airway space is critical to reducing the work of breathing. Elevated airway resistance may lead to excessive use of energy to allow for adequate ventilation. Now, all of these 15 IOPD patients have normal body weight and body height, and none of them need invasive respiratory support devices. We will continue to observe patients’ conditions and conduct prompt intervention as needed.

Our study has some limitations that warrants mention. It is difficult to have quantitative measurements in FB examination for infant patients. We have stated in the method that the tool we used in this study is FB examination, combined with clinical symptoms by a pediatric pulmonologist certificated to perform FB examination. The FB video of FB examination was recorded and analyzed fully for all patients. The airway abnormalities were diagnosed by a specialist. Adult patients can receive rhinomanometry clearly to measure resistance, quantify glottic airway and pixel size, and check vocal fold length, but this is not possible for infant patients. However, according to our FB video, the FB findings are significant and all confirmed by a specialist. The FB video of FB for I-1 and I-11 is available as Video S1. Furthermore, we have tried our best to avoid ascertainment bias by performing FB examination and confirming the abnormalities by the same pediatric pulmonologist who was independent from our study group.

We recommend airway survey for all patients with IOPD, even with very early treatment, and FB as a useful and effective tool for whole airway examination. Airway abnormalities might be the critical factors for the long-term prognosis of Pompe disease. Early diagnosis was important for better outcomes. According to our findings, we have adjusted the management of respiratory function for the patients with IOPD. They are now recommended to receive polysomnography from age 6 months and pulmonary function test from 3 years old, then follow up every 6 months. The functional tests combine with anatomic findings by FB might provide more reliable information of respiratory problems of IOPD. We will continuously do prospective follow-up in our patients with IOPD. Earlier interventions including higher ERT, early speech and occupational therapy, and night time nasal intermittent positive pressure ventilation will be considered aggressively, especially for those patients with abnormal FB findings and respiratory dysfunctions. Longer follow-up will be done to investigate more effective treatments for managing Pompe disease.

5 CONCLUSION

Even with very early and regular treatment, some airway abnormalities still occur and influence long-term outcomes of patients with IOPD. This might be due to a poorer efficacy of Myozyme in the buccal area and the upper airway. In all patients with IOPD, we recommend airway surveys by FB. Further studies will be conducted to determine the pathogenicity of this phenomenon. Long-term follow-up will be continuously performed to provide an accurate and ultimate assumption.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS


DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Wen-Jue Soong https://orcid.org/0000-0003-4607-696X

REFERENCES


**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of this article.